REMARKS

In accordance with 37 CFR 1.133(b), applicants herein below provide a complete written statement of the reasons warranting favorable action by the Office presented during the telephonic interview of May 8, 2003 (addressing the May 6, 2003 suggestions of Examiner Joynes and Examiner Page for claim amendments, stemming from the telephonic interview of April 28, 2003) and documents submitted via facsimile supporting the same. Present during the interview was Examiner Joynes, Denis Polyn, and Rita Vacca. After the May 8, 2003 telephone interview, Examiner Joynes consulted with Supervisory Examiner Page, and then called back applicants' attorney. Applicants believed that agreement had been reached with regard to all claim language based on the call. The Advisory Action of May 15, 2003 clearly indicates that there had been a miscommunication.

Each of the issues raised in the Advisory Action of May 15, 2003 was addressed during the interviews of April 28,2003 and May 8, 2003 and so are again presented in the subject interview summary.

The subject invention has been proven useful in a ten-year, multicenter, prospective, Age-Related Eye Disease Study (AREDS) conducted by the National Eye Institute (NEI) to strengthen and promote retinal health through the prevention, stabilization and/or treatment of visual acuity loss in people with particular ocular diseases. The AREDS study showed the present invention to have surprising beneficial effects over the independent use of either an antioxidant combination (i.e., Vit. A as beta carotene, Vit. C and Vit. E) or a zinc/copper combination, each of which combinations individually proved to be ineffective. That is, when compared to placebo in a large, well controlled clinical trial neither the antioxidant combination nor the zinc/copper combination, individually, proved to have a statistically significant beneficial effect on reducing the risk of vision loss.

It is through the unique combination of **6 to 10** times the RDA of vitamin A as beta carotene, **7 to 10** times the RDA of vitamin C, **13 to 18** times the RDA of vitamin E, **4 to 7** times the RDA of zinc and approximately the RDA of copper that the beneficial effects of the present invention are achieved. **An antioxidant combination (Vit. A as beta carotene, Vit. C and Vit. E), alone, proved to be ineffective** (See previously submitted, AREDS Report No. 8 titled *"A Randomized, Placebo-Controlled, Clinical Trial of High-Dose Supplementation With Vitamins C and E, Beta Carotene, and Zinc for Age-Related Macular Degeneration and Vision Loss"* (hereinafter "AREDS Report"). **The combination of zinc and copper, alone, proved to be ineffective** (See AREDS Report).

The potential toxicity of zinc and the use of copper to combat anemia induced by oral zinc therapy is known in the art. See enclosed abstracts obtained electronically from the National Library of Medicine submitted to Examiner Page via facsimile on May 20, 2003, i.e., Hoogenraad et al., ***Copper responsive anemia, induced by oral zinc therapy in a patient with acrodermatitis enteropathica***, Sci Total Environ, (1985) Mar 15:42(1-2):37-43, Botash et al., ***Zinc-induced copper deficiency in an infant***, Am J Dis Child, (1992) Jun, 146 (6):709-11, Hoffman et al, ***Zinc-induced copper deficiency***, Gastroenterology (1988) Feb, 94 (2):508-12, and Prasad et al., ***Hypocupremia induced by zinc therapy in adults***, JAMA, (1978) Nov, 10, 240(20):2166-8. The use of copper to combat anemia induced by oral zinc therapy is **not** applicants' invention. Adding the language suggested by the Office relating to zinc and copper to combat potential anemia is not necessary to distinguish the art of record. Applicants' will not make this suggested amendment in the continuation application that will be filed to cover the now cancelled method claims. This proposed language is no more relevant to the method claims than it is to the present composition claims.

Claims 1-25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gorsek, U.S. Patent Number 6,103,756, (Gorsek) alone or in view of Newsome, D. A., et al., Oral Zinc in Macular Degeneration, Arch. Ophthalmol., Vol. 106, February 1988, pp. 192-198 (Newsome). Applicants respectfully traverse the subject rejection of claims 1-25 under 35 U.S.C. 103(a).

Gorsek, a primary reference, teaches a formulation for treating macular degeneration comprising thirteen essential ingredients, e.g., vitamin C (1.5 to 100 times the %DV), vitamin E (3.3 to 67 times the %DV), vitamin A (0.2 to 4 times the %DV), which is described in Col. 2, lines 33-35 as natural carotenoids consisting of beta carotene, alpha carotene, lutein, zeaxanthin, cryptoxanthin and palmitate (which is not applicants' beta carotene), magnesium, L-taurine, selenium, bilberry extract, lutein extract, lycopene extract, alpha lipoic acid, quercetin, rutin and citrus bioflavonoids, in addition to twenty-three non-essential ingredients. Two of the foregoing non-essential ingredients of Gorsek are zinc (1.6 times the %DV) and copper (0.5 times the %DV), which are, however, essential ingredients of applicants' invention.

Gorsek does not teach the present invention or the surprising beneficial effects achieved by the specific formulation of vitamin A as beta carotene, vitamin C, vitamin E, zinc and copper of the present invention. **Rather, Gorsek teaches that zinc and copper are non-essential ingredients.** The AREDS study showed that an antioxidant combination (i.e., vitamin A in the form of beta carotene, vitamin C and vitamin E) was not effective without zinc and copper. Zinc and copper are essential ingredients in the present invention. See, for example, pages 17 and 18, paragraphs 33 and 34 of the present specification and page 1417 and 1432 of AREDS Report 8. Gorsek thereby **teaches away** from the necessity of zinc **and** copper **with** the antioxidants to achieve an effective formulation. The present invention when compared to the teachings of

Gorsek also differs in the **amount and type of vitamin A (Gorsek's natural carotenoids vs. applicants' beta carotene),** the **amount of zinc** and the **amount of copper**. For these reasons, a *prima facie* case of obviousness has not been established based on Gorsek.

Newsome teaches that the administration of 5.3 times the RDA of zinc to achieve a limited treatment effect in macular degeneration is **not** supported by the study data due to the possible toxic effects and complications of oral zinc administration (see page 192, column 1, lines 20-28). Hence, Newsome teaches that the use of high levels of zinc potentially causes more harm than good and its use is not recommended. If one were to combine, *arguendo*, the teachings of Gorsek (zinc and copper are non-essential) and Newsome (high levels of zinc cause more harm than good), this would not be applicants' invention. There is no reason or incentive provided in either reference to make this combination. (See, *In re Dow Chem.*, 837 F.2d469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). The present invention differs from this hypothetical combination in the **amount and type of vitamin A**, the **amount of zinc** (Newsome teaches away from the use of high levels of zinc as causing more harm than good) and the **amount of copper.** Even if this hypothetical combination could somehow create a *prima facie* case of obviousness, it would be overcome by the unexpected beneficial effects achieved and documented in the AREDS Report. AREDS found the present composition to provide an exceptional achievement in the preservation of vision by delaying the progression of age-related macular degeneration and vision loss (25% reduction in vision loss). Withdrawal of the rejection of claims 1-25 under 35 U.S.C. 103(a) over Gorsek or Gorsek in view of Newsome is thereby respectfully requested.

Claims 1-25 stand rejected under 35 U.S.C. 103(a) as being unpatentable over LaHaye et al., U.S. Patent Number 5,075,116 (LaHaye) in view of Gorsek further in view of Newsome. Applicants respectfully traverse the subject rejection of claims 1-25 under 35 U.S.C. 103(a).

LaHaye, a primary reference, teaches a formulation for treating macular degeneration having seven essential synergistic ingredients, i.e., vitamin C (33.3 times the RDA), vitamin E (2 times the RDA), zinc (6.7 times the RDA), copper (2 times the RDA), selenium, manganese and at least one of L-cysteine, pyridoxine or riboflavin, and as possible non-essential ingredients, vitamin A or vitamin P (rutin). As taught by LaHaye, vitamin A or vitamin P could be used as a substitute for, or in addition to, one of the seven essential "active ingredients", but they are not necessary. Since no teaching is provided in LaHaye with regard to the amount of vitamin A or vitamin P that could optionally be used, a person of ordinary skill in the art would look to the U.S. Food and Drug Administration's (FDA's) recommended daily allowance (RDA) for these vitamins. The RDA for vitamin A is 5000 IU. Applicants' invention requires approximately 6 to 10 times (30,000 to 50,000 IU) the RDA of vitamin A in the form of beta carotene. The present invention, compared to LaHaye, differs in the **amount of vitamin C** (7 – 10 times RDA vs. 33.3 times RDA), the **amount of vitamin E** (13 – 18 times RDA vs. 2 times RDA), the **amount of copper** (RDA vs. 2 times RDA), and the **amount of vitamin A** (6 – 10 times the RDA of vitamin A in the form of beta carotene vs. RDA of vitamin A). The only overlap between the ingredient ranges of LaHaye and the present invention is for zinc. Since LaHaye states that the seven essential ingredients are synergistic, why would a person of ordinary skill in the art vary the ingredients and their concentrations and still expect to obtain the described synergistic results? LaHaye, standing alone, could not possibly create a *prima facie* case of obviousness.

The proposed combination of LaHaye with Gorsek does not compensate for the previously enumerated deficiencies of LaHaye. Gorsek teaches that zinc and copper are non-essential ingredients. Gorsek also teaches the use of natural carotenoids (described in Col. 2, lines 33-35 as consisting of beta carotene, alpha carotene, lutein, zeaxanthin, cryptoxanthin and palmitate). Applicants use beta carotene, not the six component natural carotenoid mixture of Gorsek; furthermore, applicants use a much higher concentration of beta carotene (6 –10 times RDA of vitamin A as beta carotene vs. 0.2 to 4 times RDA of natural carotenoids). In addition to the foregoing, why would a person of ordinary skill in the art modify LaHaye in view of Gorsek to:

A) drop the concentration of vitamin C from 33.3 RDA to 7 –10 times the RDA;

B) increase the concentration of vitamin E from 2 times RDA to 13 –18 times RDA; and,

C) decrease the concentration of copper from 2 times RDA to RDA?

Since Gorsek teaches that both copper and zinc are non-essential ingredients, why wouldn't a person of ordinary skill in the art eliminate those two ingredients from the hypothetical combination? If one of ordinary skill in the art, for some reason not of record, added the natural carotenoids of Gorsek to LaHaye, it would be different in both composition and concentration from applicants' beta carotene. Applicants have no idea what type of composition might be created by the hypothetical combination of LaHaye in view of Gorsek, but it would not be applicants' invention. There is no reason or incentive provided in either reference to make this combination. See, *In re Dow Chem.*, 837 F.2d469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

The same is also true if the teachings of LaHaye were to be combined with the teachings of Gorsek and Newsome. All that Newsome teaches is the administration of 5.3 times the RDA of zinc to achieve a limited treatment effect in macular degeneration. There is no disclosure in Newsome relating to vitamins C, E or beta carotene, nor is there any disclosure relating to copper. Furthermore, the use of 5.3 times the RDA of zinc is **not** supported by study data in this reference due to the possible toxic effects and complications of oral zinc administration (see page 192, column 1, lines 20-28). If one were to combine, *arguendo*, the teachings of LaHaye (the deficiencies of this primary reference have been previously enumerated) and Newsome (high levels of zinc cause more harm than good), this would create some hypothetical composition that bears virtually no relationship to applicants' invention. In any event, there is no reason or incentive provided in any of the references to make this proposed combination. See, *In re Dow Chem.*, 837 F.2d469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). A *prima facie* case of obviousness has not been established based on the proposed combination of the three references. Even if a *prima facie* case of obviousness could be established, it would be overcome by the beneficial effects achieved and documented in the AREDS Report. AREDS found the present composition to provide an exceptional achievement in the preservation of vision by delaying the progression of age-related macular degeneration and vision loss (25% reduction in vision loss). Withdrawal of the rejection of claims 1-25 under 35 U.S.C. 103(a) over LaHaye in view of Gorsek further in view of Newsome is respectfully requested.

Applicants believe that claims 1, 2, 6-22 and 25-28 are patentable as written. Allowance of claims 1, 2, 6-22 and 25-28 is thereby respectfully requested.

Should there be any questions regarding this communication, please feel free to contact the undersigned at (636) 226-3340.

Respectfully submitted,

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